REMARKS/ARGUMENTS

In response to the Final Rejection mailed May 7, 2003, Applicants have amended claims 1, 13, 27, 29, 31 and 32 and present the following remarks.

The specification was objected to as not providing antecedent basis for certain language found in the original claims. The specification has been amended accordingly. Support for the amendment is found in the originally filed claims.

Claim 25 was rejected under 35 USC 112, first paragraph as not being described in the specification. Specifically, the examiner urges that fractionation of native urinary proteins are not disclosed. This rejection is traversed.

Fractionation of native proteins in a biological fluid is a feature of the present invention and is described in several places in the specification such as page 7, lines 7-8, page 9, lines 13-17 and page 11, lines 3-8 (later denaturing of originally native proteins). Many other locations refer to body fluids, which are generally made of native proteins except for degradation, disease (e.g. vCJD) and injury (e.g. burns) products. Accordingly, the rejection should be withdrawn.

Claims 26 and 28 were rejected under 35 USC 112, first paragraph, as not being described in the specification. Specifically, the filtration limits of a normal kidney are not given. This rejection is respectfully traversed.

It should be noted a normal kidney does not have a strict filtration limit where molecules differing by one Dalton can be separated. Very high concentrations in the blood can result in a small amount of high molecular weight proteins "leaking" through. It should be noted that the same is true for most artificial filters also. Also, because biological systems such as a kidney are somewhat variable and flexible, the filtration limit is likewise the same. Nonetheless, the terms are clear to those skilled in the art. See the discussion in the paragraph bridging pages 2 and 3 of the specification for further explanation. The goal of the present invention is to fractionate proteins which came from the blood from those higher

molecular weight proteins which apparently came from other sources, e.g. bladder, ureter, kidney, microorganisms, etc.)

The examiner has contended that above about 30,000 daltons is not the disclosed filtration limit. To avoid confusion, the claims have been amended to clarify that the fractionation process is being recited in this claim and that applicants are not defining a natural normal kidney. While the filtration limit of a normal kidney is generally greater than 30,000 daltons, the specification includes an example where a separation of proteins around 30,000 daltons was used. The claim attempts to cover this feature.

Claims 1, 3-19 and 25-38 are rejected under 35 USC 112, second paragraph, as being indefinite in the recitation "above about", antecedent basis for "the filtration limits of a normal kidney" and "plural specific predetermined proteins". To the extent that these remain an issue, the rejection is respectfully traversed.

The term "greater than" has been substituted for "above" to clarify that the claim recitation does not refer to location. The term "the" has been deleted to avoid an alleged lack of antecedent basis. The term "plural specific predetermined proteins" is clear within the context of the present application. Applicants decided which specific proteins to remove before or after fractionation so that these specific proteins do not interfere with or reduce the sensitivity of further analysis. See page 6, lines 10+, page 22, lines 3+, page 29-31 of the specification. The exemplified method for removing "plural specific predetermined proteins" is by way of an affinity column with plural antibodies (and or other receptor) attached where each antibody (or other receptor) binds to and removes it specific predetermined protein binding partner. See page 42, line 23 to page 43, line 9. This language is intended to distinguish over non-specific adsorption of many proteins where one does not know which proteins are adsorbed ahead of time.

The examiner has questioned whether claim 32 depends on claim 1 or should be a separate claim. Claim 32 is a product produced by the process of claim 1. Process claim 1 recites other components or steps but it is the recovered "first fraction" which is claimed in claim 32. Claim 32 has been amended to further emphasize this.

Claims 1, 3-5, 30-34 and 36 were rejected under 35 USC 102(b) as being anticipated by Liu et al in light of Gilbert et al. Liu et al is cited as showing the fractionation of urine proteins and the recovery of alpha-1-antitrypsin. The rejection is respectfully traversed.

The Liu et al method removes small molecules and then fractionates the remaining proteins into many size fractions. The reference does not disclose a single liquid composition that has all of the mid-range proteins without the small molecules (less than about 3kDa) and without the large proteins (greater than the filtration limits of a kidney). While Liu et al produces many fractions, no single fraction corresponds to the fraction recited in the claims. At best, one might consider Liu et al as making a composition that is a small subset, or even a single molecule, which might be found within the fraction made by the present invention.

On page 13 of the Office action, the examiner appears to argue that recovery of this small subset or even a single molecule within the broader range claimed anticipates the claims. While applicants disagree with this interpretation, claim 1 was amended to highlight this difference. Claim 1 recites that the fraction contains substantially all of the proteins within the claimed molecular weight range, which were present in the original biological sample. This excludes single molecules and small subset fractions such as those recovered from a chromatography column. The goal of the invention is to make this fraction as a way of avoiding many of the non-plasma filtration originating proteins found in urine. The analytical separation is later performed, by for example 2-D gel electrophoresis, on the plasma-originating proteins.

Specific steps b), c) and d) in claim 1 are at least partially not disclosed by Liu et al. Liu does not actively seek to form a single liquid composition with substantially all of the proteins from the sample within the claimed molecular weight range as recited in claim 1 step b). Even if such were accidentally made, Liu et al does not recover this "first fraction" as is required by claim 1 step c). Both of these steps are preparative. Claim 1 step d) is analytical and also is not disclosed because step d) recites determining plural protein components in the fraction. Liu et al only determines one protein by their analytical step. While Liu et al may see multiple peaks on an electropherogram, they determine only one

protein in each step. By contrast, the specification examples detect and quantify hundreds or thousands of proteins simultaneously in the analytical step.

Accordingly, Liu et al never forms the claimed fraction in its totality or any fraction even close to the fraction. The fact that single molecules are isolated by their method does not indicate the formation of the claimed fraction. Therefore, this rejection should now be withdrawn.

Claim 7 was rejected under 35 USC 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of O'Donnell et al. This rejection has the same deficiencies as the rejection under 35 USC 102(b) above with O'Donnell not compensating for these deficiencies. Therefore, for the reasons given above, this rejection should be withdrawn.

Claims 8 and 9 were rejected under 35 USC 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Anderson et al. Anderson et al is cited to show the pretreatment centrifugation steps. However, such a showing does not compensate for the basic deficiencies of the rejection under 35 USC 102(b) above and the fractions formed are not those claimed. Therefore, for the reasons given above, this rejection should be withdrawn.

Claims 10, 11 and 19 were rejected under 35 USC 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Opiteck et al. Opiteck et al discloses downstream techniques, which are done to analyze the sample after fractionation. Opiteck et al does not compensate for the basic deficiencies of the rejection under 35 USC 102(b) above regarding the fractions formed as presently claimed. Accordingly, , for the reasons given above, this rejection should be withdrawn.

Claims 12, 15-17, 27 and 29 were rejected under 35 USC 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Hage et al. In addition to the lack of compensating for the deficiencies cited above, Hage et al alone or in combination with Liu et al and Gilbert et al does not provide any teaching similar to the recitations in claim 27 and 29.

There is no suggestion to recover a second fraction that contains substantially all of the proteins in the biological fluid, which have molecular weights above the filtration limits of the kidney. Between the first fraction and the second fraction, essentially all of the proteins are divided and accounted for. Salts, small organic compounds and short polypeptides (not considered regular "proteins" in this application) may appear in a third fraction, which is discarded in the application examples.

The rejection comments are silent as to these recitations. Even if one considers the uncollected high molecular weight throw-away fraction in Liu et al to be similar to the claimed second fraction, the references do not teach recovering this fraction and certainly not determining the proteins in said second fraction as is recited in claim 27. Thus, the rejection should be withdrawn for this particular claim.

As a separate issue, the use of an affinity column containing plural specific binding agents that bind to corresponding predetermined proteins in the sample is not mentioned anywhere in any of the references. Affinity chromatography is taught to have only one antibody or other ligand-binding partner on the column. This affinity chromatography can only purify the protein ligand specific for the antibody/binding partner. There is simply no teaching of having two or more antibodies/etc. on the same column.

It should be noted that Hage et al is a review of techniques to purify a particular protein. For affinity chromatography taught by Hage et al, one wishes to purify and recover a single protein. There would be no motivation to have plural antibodies to different proteins because that would co-bind at least both proteins and thereby defeat the purpose of purification. By contrast, applicants are attempting to do the opposite by removing a few predetermined abundant proteins so that the fraction containing many proteins can be recovered. Thus, the rejection should be withdrawn for this specific claim.

Claims 13, 14 and 37 were rejected under 35 USC 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of McCombs et al. McCombs et al is cited to show an antibody against alpha-1-antitrypsin. However, such a showing does not compensate for the basic deficiencies of the rejection under 35 USC 102(b) above and the fractions formed

are not those claimed. Therefore, for the reasons given above, this rejection should be withdrawn.

Claims 6 and 18 were rejected under 35 USC 103(a) as being unpatentable over Liu et al in light of Gilbert et al in view of Furst et al. While Furst et al may teach various sedimentation techniques, there was no suggestion to combine this technique with the fractionation techniques of Liu et al. Liu et al uses liquids, not fluids with particles in them. With no need to separate particles in Liu et al, one lacks motivation to add a particle fractionation technique to the basic technique. In any event, such a showing does not compensate for the basic deficiencies of the rejection under 35 USC 102(b) above and the fractions formed are not those claimed. Accordingly, for the reasons given above, this rejection should be withdrawn.

In view of the above amendments and comments, the claims are now in conditions for allowance and applicants request a timely Notice of Allowance be issued in this application. If any issues or questions remain, the examiner is encouraged to call the undersigned at the telephone number below.

The commissioner hereby is authorized to charge payment of any fees under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,

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